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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,460	01/17/2006	David Alland	UMD-0112	4649

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EXAMINER

MYERS, CARLA J

ART UNIT	PAPER NUMBER
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1634

NOTIFICATION DATE	DELIVERY MODE
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02/05/2008

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary

Application No.

10/540,460

Applicant(s)

ALLAND ET AL.

Examiner

Carla Myers

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/19/07.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) 8-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 6-22-05 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>6-22-05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-7 in the reply filed on November 19, 2007 is acknowledged. The traversal is on the ground(s) that inventions of Group I and II were examined in the PCT application and therefore the restriction requirement is not consistent with the search conducted at the PCT stage. It is further asserted that because Groups I and II were searched at the PCT stage, no search burden would be required to examine both groups together in the present application. This is not found persuasive because the determination of lack of unity of invention may be made at the National stage and is not controlled by the findings at the PCT stage. As set forth in MPEP 1893.03(d), "If the examiner finds that a national stage application lacks unity of invention under § 1.475, the examiner may in an Office action require the applicant in the response to that action to elect the invention to which the claims shall be restricted. Such requirement may be made before any action on the merits but may be made at any time before the final action at the discretion of the examiner."

Further, A 371 case is considered to have unity of invention only when there is a technical relationship among those inventions involving one or more of the same or corresponding technical features. In the instant application, the technical feature linking the claimed inventions of a hairpin primer for amplifying a 30 to 90bp sequence and having a 3' terminus located at a SNP was known in the art at the time the invention was made, and was specifically disclosed by Nazarenko (U.S. Patent No. 6,090,552) as set forth below. Further, regarding claim 8, Nazarenko (cols.52-54 and

Table 5) discloses a primer that is hairpin shaped and is capable of amplifying a 30 to 90bp sequence, wherein the primer has a 3' nucleotide that terminates at a polymorphic position. With respect to the limitation in claim 8 of "kits," in the absence of any recitation in the claims or any direction in the specification to the contrary, the recitation of kit reads on component parts capable of being assembled or a plurality of elements grouped together as a kit. Accordingly, the word "kit" does not impart any additional special structural or functional features which distinguishes the claimed products over the hairpin primer of Nazarenko. Accordingly, there is no special technical feature linking the recited groups, as would be required to fulfill unity of invention

The requirement is still deemed proper and is therefore made FINAL.

Priority

2. If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, a petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. However, Applicant is still required to submit the reference in compliance with 37 CFR

1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS.

See MPEP § 201.11.

In particular, an Application Data sheet with a reference to the priority applications should be filed or the first line of the specification should be amended to recite, for example: This application is the National Stage of International Application PCT/US03/41136, filed December 24, 2003, which claims the benefit of U.S. Provisional Application 60/437,165, filed December 27, 2002.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are indefinite over the recitation of the phrases "lower amplification efficiency", "delayed threshold cycle" and "a difference in the amount" because these phrases are relative terminology and the claims do not set forth what the phrases are being compared to or with. These phrases are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, one cannot ascertain what constitutes a lower amplification efficiency since the claims do not recite what the amplification efficiency is being compared with.

Claims 2-4 are indefinite over the recitation of "the nucleic acid sequence" (claim 2) because this phrase lacks proper antecedent basis. While the claims previously refer to a nucleic acid molecule, the claims do not previously refer to a "nucleic acid sequence."

Claim 4 is indefinite over the recitation of "the PCR reaction" because this phrase lacks proper antecedent basis. While the claim previously refers to PCR, the claim does not previously refer to a "PCR reaction."

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Nazarenko et al (U.S. Patent No. 6,090,552, 7/18/2000) as evidenced by GenBank Accession No. NM_000025 (April 1999).

Nazarenko (see column 27; and 52-54, Example 10) teaches a method for detecting the presence of a single nucleotide polymorphism or a mutation in a target nucleic acid in an organism wherein the method comprises: (i) amplifying a nucleic acid sequence using a hairpin primer, wherein the hairpin primer terminates at a polymorphic position, such that the 3' nucleotide of the hairpin primer is located at the position of the single nucleotide polymorphism or mutation; and (ii) measuring the amount of amplification product wherein a decrease in the amplification product is indicative of the

presence of a polymorphism or mutation (i.e., a mismatch between the hairpin primer and the target nucleic acid). Nazarenko (column 27) teaches that in the method of allele-specific PCR, "(u)nder the appropriate reaction conditions, the target DNA is not amplified if there is a base mismatch."

Regarding the recitation in the claims that the method is one which amplifies a 30 to 90 base pair nucleic acid molecule of an organism, the method exemplified by Nazarenko results in the amplification of 101 base pairs of the B3AR (i.e., adrenergic receptor beta-3 nucleic acid / ADRB3) nucleic acid. Thus, the method of Nazarenko is one in which 30 to 90 bp of a nucleic acid molecule of an organism is amplified since amplification of a 101 base pair region necessarily includes the amplification of 30 to 90 base pairs. Note that the claims do not require the use of a second primer located at a particular distance from the hairpin primer and do not define the length of an amplification product. The fact that the method of Nazarenko results in the amplification of 101 bp of an organisms' ADRB3 nucleic acid is evidenced by the teachings of GenBank Accession No. NM_000025 wherein the nucleotide positions to which the forward and reverse primers of Nazarenko (Table 5) hybridize are disclosed. Specifically, the forward hairpin primer of Nazarenko hybridizes to nucleotides 368-387 of B3AR nucleic acids, and the reverse primer of Nazarenko hybridizes to the inverse complement of nucleotides 449-468 of B3AR, thereby generating a product containing 101bp (and thus 30 to 90bp) of an organisms' B3AR nucleic acid. Note that the GenBank reference is cited only to show what is inherent to the teachings of Nazarenko.

Regarding claim 2, in the method of Nazarenko, the nucleic acid is amplified by PCR (col. 53).

Regarding claim 4, Nazarenko teaches detecting PCR amplification products at the completion of the PCR assay (col. 53-54).

Regarding claim 5, the hairpin primers exemplified by Nazarenko comprise DNA (Table 5).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable Nazarenko.

The teachings of Nazarenko are presented above.

Regarding claim 3, Nazarenko exemplifies methods wherein the hairpin primer comprise DNA (Table 5), but does not exemplify methods wherein the hairpin primer comprises RNA. However, Nazarenko (col. 17, lines 36-40) does teach that the hairpin primer may be DNA or RNA.

Regarding claim 6, Nazarenko (col. 53-54) exemplifies methods using allele-specific hairpin primers wherein the PCR amplification products are detected at the completion of the PCR assay, but does not exemplify methods using allele-specific hairpin primers wherein the PCR amplification products are detected using real-time PCR. However, Nazarenko does teach that in methods in which the amplification product is formed using a hairpin primer, the amplification product can be detected by real-time PCR (see col. 43 and 48). It is stated that real-time PCR detection provides the advantages of allowing researches to perform the method in closed tubes, thereby eliminating the risk of carry-over contamination, simplifies the detection assay, and permits quantification of the amplification products over a wide dynamic range. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko so as to have detected the amplification products using real-time PCR in order to have provided an effective means for monitoring the allele-specific amplification reaction which would simply the detection method, reduce cross-contamination and allow for a highly accurate quantification of the amplification products.

6. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable Nazarenko in view of Tyagi (U.S. Patent No. 6,365,729; cited in the IDS).

The teachings of Nazarenko are presented above.

Nazarenko exemplifies methods wherein the hairpin primer comprises DNA (Table 5) and teaches that the hairpin primer may also comprise RNA or may be modified in the base, sugar or phosphate backbone (co. 17, lines 36 to col. 18, line 11). However, Nazarenko does not exemplify methods wherein the hairpin primer comprises PNA.

Tyagi (col. 3 and 6) teaches a method of allele-specific PCR using hairpin primers. Tyagi (column 2) teaches that "if the binding of the primer in the tube to the target sequence creates a mismatched 3'-terminal nucleotide, then the primer cannot be efficiently extended by incubation with DNA polymerase. Amplification of the mismatched template is significantly delayed." Tyagi (column 6) further teaches that hairpin primers used for allele-specific PCR may contain PNAs.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko so as to have performed the allele-specific PCR method using hairpin primers that contain PNAs in view of the well known benefits provided by PNAs of enhancing the stability of hybridization and improving the ability to distinguish between perfectly matched and mismatched sequences. Thereby, one would have been motivated to have used PNA hairpin primers in order to have provided a highly sensitive and effective method for detecting the presence of a polymorphism or mutation.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634